16:03:46 OCA PAD INITIATION - PROJECT HEADER INFORMATION 06/29/88

Active

Project #: [redacted]
Center #: R6345-1A0
Cost share #:
Center shr #:
Rev #: 0
OCA file #:
Work type : RES
Document : GRANT
Contract entity: GTRC

Contract #: [redacted] R01 CA43806-02
Prime #:
Mod #:

Subprojects ? : N
Main project #:

Project unit: CHEM Unit code: 02.010.136
Project director(s):
[redacted] CHEM
[redacted] CHEM

Sponsor/division names: [redacted] DHHS/PHS/NIH [redacted] NATL INSTITUTES OF HEALTH
Sponsor/division codes: [redacted] 08 [redacted] 01

Award period: [redacted] 880701 to 890630 (performance) 90930 (reports)

Sponsor amount	New this change	Total to date
Contract value	123,842.00	123,842.00
Funded	123,842.00	123,842.00
Cost sharing amount		0.00

Does subcontracting plan apply ?: N

Title: [redacted] BIOOXIDATION OF ARYLALKYL HYDROCARBONS

PROJECT ADMINISTRATION DATA

OCA contact: [redacted] 894-4820

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Security class (U,C,S,TS) : [redacted]
Defense priority rating :
Equipment title vests with: Sponsor

ONR resident rep. is ACO (Y/[redacted]
supplemental sheet
GIT X

Administrative comments -
INITIATION

12 / 88

GEORGIA INSTITUTE OF TECHNOLOGY
OFFICE OF CONTRACT ADMINISTRATION

NOTICE OF PROJECT CLOSEOUT

Date 8/24/89

ect No. G-33-614 Center No. R6345-1A0

ect Director L. M. Tolbert School/Lab Chemistry

sor DHHS/PHS/NIH

ract/Grant No. 5 R01 CA43806-02 GTRC XX GIT ____

e Contract No. N/A

e Biooxidation of Arylalkyl Hydrocarbons

ctive Completion Date 6/30/89 (Performance) 9/30/89 (Reports)

eout Actions Required:

None
Final Invoice or Copy of Last Invoice
Final Report of Inventions and/or Subcontracts
Government Property Inventory & Related Certificate
Classified Material Certificate
Release and Assignment
Other ____

udes Subproject No(s). ____

roject Under Main Project No. ____

inues Project No. G-33-606 Continued by Project No. G-33-666

ribution:

Project Director
Administrative Network
Accounting
Procurement/GTRI Supply Services
Research Property Management
Research Security Services

X Reports Coordinator (OCA)
X GTRC
X Project File
Z Contract Support Division (OCA)
___ Other ____

6-33-614

SECTION IV **PROGRESS REPORT SUMMARY**	GRANT N[illegible] CA43806-03	
PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR [illegible] M. Tolbert	PERIOD COVERED BY THIS REPORT FROM	THROUGH
APPLICANT ORGANIZATION Georgia Tech Research Corporation	July 1, 1989	June 30, 1990

TITLE OF PROJECT *(Repeat title shown in item 1 on first page)*
Bio-oxidation of Arylalkyl Hydrocarbons

(SEE INSTRUCTIONS)

1. **Proposed Research.** No significant changes in the scope of the research are anticipated from that proposed in the original application and as modified in the 1988 report. This reflects our progress in achieving the aims of developing models for side-chain vs. ring attach in radical cation intermediates. However, we will complete studies on pyridine nucleophiles which provide insight into the role of nucleophile basicity in the partition. Also, in order to provide a complete picture of the decomposition pathways, we will further investigate the reaction manifold which results in dealkylation of 9,10-dialkylanthracenes to yield anthraquinone as the ultimate oxidized product.

2. **Progress.** As outlined in our 1988 report, we have included additional oxidants in our studies, particularly those used as model compounds for cytochrome P450. These particularly include (tetraphenylporphinato)iron oxide (TTP-Fe=O), the so-called "ferryl complex." We have discovered significant differences between reaction pathways with this oxidant and with tris(phenanthroline)iron(III) ($Fe(phen)_3$), our model one-electron oxidant. These differences, however, show up at the secondary oxidation stage, that is, in the oxidation of the initially formed hydroxymethyl intermediate. This intermediate undergoes further oxidation by $Fe(phen)_3$ in <u>non-aqueous solvents</u> to yield formaldehyde and 10-methylanthrone. The significance of this result rests in the requirement that such reaction involve carbon-carbon bond cleavage. These studies are preliminary, and the biological relevance of formaldehyde generation in the overall mutagenicity of dimethylanthracene derivatives has not yet been ascertained. Howevever, we do observe that TPP-Fe=O also produces oxidative demethylation with formaldehyde formation as well. We previously had noted an anomalous irreversible cyclic voltammetric wave in the oxidation of 9-(hydroxymethyl)-10-methylanthracene, which we attributed to an internal solvation to yield a spiroepoxide intermediate. This additional evidence for anomalous chemical reactivity for the hydroxymethyl compound has relevance to the whole issue of mechanism in arene epoxidation, which we are currently elaborating through product studies.

The product of oxidative carbon-carbon bond cleavage, i. e., 10-methyl-9-anthrone undergoes further oxidation to 10-methyl-10-hydroxy-9-anthrone and 9,10-anthraquinone, the latter involving a second demethylation step. Obviously, such demethylation is a salient feature of metabolism of meso-alkylanthracene derivatives, and we are elucidating the details of this reaction pathway as a function of oxidant.

As part of our studies on the partition between side-chain deprotonation and ring attack, we have investigated the effect of basicity on that partition, using pyridines as our basic nucleophiles. This takes advantage of some work of Cavalieri, who observed such duality in the reaction of 9-methylanthracene with pyridine to yield either 9-(N-pyridinium)-10-methylanthracene or 9-(N-pyridiniummethyl)anthracene. By using substituted pyridines, we were able to obtain a correlation of the log ratio of products to the Hammett substituent constant and thus evaluate the effect of basicity on the partition. This correlation is also dependent upon the quality of the pyridines, which yield one ratio with anhydrous material and another ratio with wet material. We believe that water acts as an intermediate proton relay in this reaction.

Progress (cont'd)

Our studies in 1,4-dialkylnaphthalene oxidations have been straightforward, if less surprising. Due to a lack of steric inhibition to planarity, the reaction pathway is dominated by proton loss from the side chain and formation of hydroxyalkyl products.

In summary, our focus on radical-cation deprotonation reactions continues to provide a useful framework for investigating both enzymatic and biomimetic oxidation of anthracenes. Our goal, to develop a dependable chemical model for radical cation reactivity in enzyme active sites, appears attainable.

Publications (from NIH support):

Laren M. Tolbert and Rajive K. Khanna, "Dramatic Solvent and Stereoelectronic Effects in a Biomimetic Oxidation: 9.10-Dialkylanthracenes", J. Amer. Chem. Soc., 1987, 109, 3477.

Laren M. Tolbert, Rajive K. Khanna, Sarath E. Sirimanne, Ann E. Popp, and Larry A. Bottomley, "The Effect of Water on Radical Cation Deprotonations: 9,10-Dimethylanthracene", J. Amer. Chem. Soc., submitted.

Laren M. Tolbert, Rajive K. Khanna, Leslie A. Gelbaum, Ann E. Popp, and Larry A. Bottomley, "Stereoelectronic Effects in the Deprotonation of Arylakyl Radical Cations: meso-Ethylanthracenes", J. Amer. Chem. Soc., submitted.

Meetings and Symposia: (from NIH support)

"Structural Constraints in Proton Transfer of Photoexciated Naphthols", 40th Southeast Regional Meeting, American Chemical Society, Atlanta, GA, September 9, 1988.

"Regioselectivity in 1,4-Dialkylnapthalene Deprotonations", 40th Southeast Regional Meeting, American Chemical Society, Atlanta, GA, September 9, 1988.

"The Excited-State Acidities of Substituted Cyano-2-naphthols,", 196th National Meeting, American Chemical Society, Los Angeles, California, September 26, 1988.

"The Excited-State Acidities of Substituted Cyano-2-naphthols,", 196th National Meeting, American Chemical Society, Los Angeles, California, September 26, 1988.

"The Effect of Water on Radical Cation Deprotonations: 9,10-Dimethylanthracene", Third Chemical Congress of North America, Toronto, Canada, June 9, 1988.